# UNITED STATES PATENT AND TRADEMARK OFFICE

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/709,691 | 05/24/2004 | Itzhak Bentwich | 050992.0400.01USCP | 3690 |

| 37808          7590          06/23/2008 | EXAMINER |
|---|---|
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on _17 March 2008_.

2a)☒ This action is **FINAL**.          2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) _23,25,31 and 33_ is/are pending in the application.

   4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _23,25,31 and 33_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

   Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

   Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   a)☐ All   b)☐ Some * c)☐ None of:

   1.☐ Certified copies of the priority documents have been received.

   2.☐ Certified copies of the priority documents have been received in Application No. _____.

   3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

   * See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
   Paper No(s)/Mail Date _3/17/08_.
4) ☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 3/17/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/19/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 3/17/08 claims 23, 25, 31, and 33 are pending and under consideration.

### *Information Disclosure Statement*

The information disclosure statement filed 3/17/08 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the title of each publication listed in the information disclosure has not been provided. See 37 CFR 1.98(b)(5).

It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

### *Claim Rejections - 35 USC § 101 and 112, First Paragraph—maintained*

Claims 23, 25, 31, and 33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a credible asserted utility.

The claims are drawn to isolated polyribonucleotide sequences, 22 and 91 nucleotides in length, referred to therein as SEQ ID NO: 348 and 423864, respectively. The application further claims the complements of said sequences and DNAs of the same length encoding said sequences in addition to expression vectors thereof.

In the Remarks filed 6/29/07, Applicant states SEQ ID NO:348 is capable of targeting mRNAs of the human gene SERPINH1 as well as other unrelated genes. In the remarks filed 3/17/08, Applicant states the claimed nucleic acids regulate translation of mRNAs from the gene MGAT5. Thus, the claimed nucleic acids have been asserted to be capable of targeting multiple different genes.

In support of claims 23 and 25, as now written, Applicant points to Table 7, lines 312, 839-313, 772; paragraph 0044; paragraph 0047; and paragraphs 0143-0147.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification teaches a bioinformatic method for detecting putative miRNA-like precursor sequences in the genome of an organism. Further bioinformatics processing is then used to predict the single stranded miRNAs likely produced from such sequences. Finally, the sequences of the predicted miRNAs are compared to sequences of known genes to identify potential targets and possible biological functions of the miRNAs.

While the specification teaches miRNA prediction, support is not readily found showing that the claimed miRNAs are actually produced in any cell or organism, or even if produced artificially, would lead to any biological effect of any immediate, real world value. No biologically relevant data, nor any intrinsic or extrinsic evidence is found in the instant application confirming any of the asserted utilities.

While the claimed nucleic acids would have a specific and substantial utility if said nucleic acids in fact inhibit a known gene having a known function, there is no direct or indirect evidence that the claimed nucleic acids, in fact, inhibit the expression or translation of any gene, much less the genes said to be specifically targeted by the claimed nucleic acids.

Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets. Neither the accuracy nor false-positive rates of the algorithm used for prediction have been made of record, and there is absolutely no evidence that the bioinformatically predicted sequences, which typically possess much less than 100% complementarity with the predicted target, have the utility asserted by the computer prediction method. Even if the level of complementarity is typical of mammalian miRNAs, the assertion that a bioinformatically predicted miRNA will inhibit a specific gene would be deemed credible only if there were sufficient evidence to indicate one of skill would believe the predicted utility was more than likely correct even without any corroborating experimental evidence. Currently, the Examiner finds no such evidence in the prior art or application.

Post-filing art indicates that while prediction software and bioinformatics methods

significantly narrow the field of possible sequences, they do not substitute for or render

unnecessary the need for biological validation.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for

these types of prediction programs is the degree of sequence complementarity between a miRNA

and a target UTR, including the presence of a consecutive string of base pairs at the 5' end of the

miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site.

On average, 200 genes are predicted to be regulated by a single miRNA. The authors further

state that reviewing the data provided by these algorithms determining candidate targets

uncovers the entire gamut of gene categories, such as transcription factors, protein kinases,

vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias

towards one particular function.

Bentwich (2005) *FEBS Lett.* 5904-5910 teaches that biological validation is necessary to

raise the specificity and sensitivity of microRNA prediction algorithms, implying that predictions

based on such algorithms need validation and that prediction does not guarantee that such a

sequence exists or has the function assigned to it by the software.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets

from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. and

Bentwich teach that validating the true biological function of any predicted miRNA sequence

requires analyzing miRNA expression patterns, as well as testing the effects of miRNA

overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no

evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences or complements thereof.

### *Response to Arguments*

To be clear, the rejection herein and going forward is based primarily on a lack of credible asserted utility.

The claimed nucleic acid sequences are said by Applicant to regulate the expression of one or more known genes. In this respect, the asserted utility is specific and substantial. However, the assertion is not credible, as previously explained. There is substantial evidence to indicate that, at the time of filing, one of skill would have had reason to doubt the objective truth of these statements, given the proposed target was bioinformatically predicted, the accuracy and/or false positive rate of the bioinformatic prediction method was and remains unknown, and given that no experimental data is available to confirm the predicted activity. The claimed sequences are significantly less than 100% complementary to the predicted targets, and, operate, according to the applicant, by standard miRNA-guided mechanism to regulate expression. However, there is no evidence in the prior art or application to show that each and every miRNA-like hairpin predicted by the instant algorithm in fact regulates expression of a gene. Indeed, miRNA-like, non-translated hairpin RNAs may have any number of different biological activities in the cell, known or yet-to-be discovered. The fact that several miRNAs have been biologically validated using actual in vitro assay does not necessarily mean that each miRNA-like hairpin and proposed maturation product thereof regulates a gene.

Applicant's arguments and the Declaration under 37 CFR 1.132 filed 3/17/08 have been fully considered but are not persuasive for the reasons enumerated below.

In previous Office Actions, the Office has presented evidence suggesting there would have been reason at the time of filing to doubt the objective truth of the asserted utility. Further evidence is presented herein.

In brief, the instant application claims bioinformatically predicted preprocessed and mature miRNA sequences corresponding to SEQ ID NO:348 and 4233864, respectively. Applicant asserts one of skill would more likely than not conclude the claimed nucleic acids may be used to modulate the expression of a specific gene. Specific and substantial utility is thereby asserted based on bioinformatic data. The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function. Function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived therefrom by Dicer-catalyzed processing, which information is mined from raw genomic sequences.

At issue, then, is whether one of skill would more likely than not believe the nucleic acids predicted by Applicant's algorithm, such as the sequences now claimed, would have the specific and substantial utility predicted by the program.

1. The Declaration under 37 CFR 1.132 filed 3/17/08 has been fully considered, but is insufficient to overcome the rejection of claims in view of the totality of the evidence in the pre- and post-filing art. Though made by a proclaimed expert in the art, and containing sound scientific reasoning, the Declaration represents nothing more than an opinion. While the declaration quantifies the effectiveness of other miRNA prediction algorithms, the declaration does not directly quantify the accuracy and/or false positive/false negative rate of the Inventor's algorithm, the program in question.

Instead, the Declaration attempts to show the veracity of the instant prediction

software by comparison to related prediction programs. Though unclear from the

declaration, the assertion appears to be the instant algorithm is at least as effective as

prior art algorithms. However, post-filing art (cited below) indicates it is difficult if

not impossible to compare different algorithms without comparing their output using

a common dataset, which does not appear to have been done here. The Declaration

provides no experimental evidence validating either the predictive quality of the

instant algorithm or the utility of the instantly claimed sequences. Such evidence if

collected in a statistically relevant manner would be indicative of the accuracy of the

algorithm. While declarant describes the accuracy of related miRNA prediction

programs in detail, there is no discussion of the accuracy of the instant miRNA

prediction program, which is the subject of this application. The determinative factor

is the accuracy and false positive rates associated with the program used to predict the

instantly claimed miRNAs. Comparing the performance of this program to any other

is difficult when the programs have not been run on identical data sets and when there

is no objective experimental data substantiate the claims of the declarant.

2. The Declaration similarly fails to address the utility of SEQ ID NO:4233864 or the

   isolated nucleic acids complementary to either SEQ ID NO:348 or 4233864. The only

   perceived utility of the complements would be to either inhibit or detect the

   bioinformatically predicted miRNAs themselves. However, there is absolutely no

   evidence, beyond the algorithm, that the claimed miRNAs are biologically active in

   any manner, or even expressed by any cell. Thus, the complements lack both

substantial and credible utility since there is no evidence the targets of these complements have any utility or that any information of immediate, real-world value could be obtained from the use of sequences complementary to the claimed miRNAs. As for sequences less than 100% complementary to the claimed nucleic acids, there is no evidence beyond bare assertion that any of these sequences would have any utility, specific, substantial or credible. Here, the utility is unknown and there is no assurance any would ever be found.

3. The question remains whether the bioinformatically predicted miRNAs now claimed would, more likely than not, have the utility asserted. The answer lies in the predictive quality of the program used to identify the miRNAs and their target sites. A quantifiable value is not readily apparent to the Examiner from the facts of record. Indeed, the Examiner is unable to find any disclosure by the inventor either in the instant application or in the pre- or post-filing art clearly articulating the sensitivity or false positive rate of the instant algorithm. A simple statement supported by actual experimental evidence, showing the algorithm correctly predicts an miRNA and its activity more than half of the time and has an acceptable false positive rate would be sufficient to overcome the instant rejection.

4. Currently, however, neither the Declaration nor the specification addresses this question directly or completely. Accuracy would depend on several factors, including but not limited to the accuracy of the HAIRPIN DETECTOR and the accuracy of the DICER-CUT LOCATION DETECTOR. At paragraph 241, the specification states the algorithm has the ability to detect real target genes with 47% accuracy. This

would not appear to meet the credibility standard of more likely than not. The predicted miRNA may hybridize to countless numbers of different genes. The proposed target is simply a starting point for further research.

5.  Further, it would appear from the teachings in the specification that multiple determinants govern the selection process.

6.  Critical to the determination of whether the asserted utility is credible is the false positive rate of the instant prediction program. This information is not found in the instant application. Comparative algorithms used in the art are said to have false positive rates of between 22% and 39%. See Bentwich et al. (2005) *FEBS Lett.* 579:5904-5910, page 5907; and the Declaration, Point 4. See also Martin et al. (2007) *J. Biosci.* 32:1049-1052 at page 1049, 4th full paragraph.

7.  Martin et al. (2007) *J. Biosci.* 32:1049-1052, reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by

miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.

8. The post-filing art suggests that it is difficult to estimate the true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known. See Maziere et al. (2007) *Drug Discovery Today* 12:452-458, page 457. Maziere et al. in their article entitled "Prediction of miRNA Targets," further state that comparison of miRNA prediction efficiencies among different programs is not currently possible because many of the programs are not available for download and use on a common dataset; thus, Maziere et al. cast doubt on the reliability of the statements made in the Declaration, comparing similar programs to that used by the Inventor. Again, no evidence has been presented by Declarant directly comparing the output of the instant algorithm with the other cited programs when presented with a common dataset. Thus, there is no objective evidence to corroborate Declarant's opinion.

9. Smalheiser et al. (2006) *Methods Mol. Biol.* 342:115-127 in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential importance of mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential

mRNA targets from being effectively silenced by the RNA-induced silencing

complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs

interact with their targets via "short seeds," complementary regions of 6-8

nucleotides, but, instead, may interact via "long" seeds and perfect matches (page

115-6), and because new miRNAs are constantly being discovered this list of binding

determinants may not be complete.

10. Thus, multiple factors are involved in miRNA-target binding and recognition.

11. Thus, in view of the totality of the evidence, one of skill would have reason to doubt

the objective truth of the asserted utility. While the instant algorithm provides a list of

putative miRNAs and corresponding target sites, there is reason to question whether

the bioinformatic algorithm used to produce this list correctly identifies an miRNA

and its function (i.e., at least one biological function) with minimally acceptable false

positive and false negative rates such that one of skill would believe the miRNA

would, more likely than not, inhibit the gene predicted by the software. Without

experimental validation or any verifiable evidence of the accuracy and error rates of

the instant program, and in view of the state of the art at the time of invention, one of

skill would reasonably question the certainty of the prediction at the time of filing.

12. The skilled artisan would be led to believe only that the instantly claimed nucleic

acids require further research to verify the asserted utility.

***

Claims 23, 25, 31, and 33 are also rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by either a specific, substantial, and

credible asserted utility or a well established utility for the reasons set forth above, one skilled in

the art clearly would not know how to use the claimed invention.

*Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of

time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing

date of this final action.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144.

The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for

the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated

information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner, AU1635
June 13, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635